Primary breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

Pestalozzi, B ; Castiglione, M ; ESMO Guidelines Working Group

DOI: https://doi.org/10.1093/annonc/mdn071

Annals of Oncology 19 (Supplement 2): ii7–ii10, 2008
doi:10.1093/annonc/mdn071

Primary breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

B. Pestalozzi[1] & M. Castiglione[2]
On behalf of the ESMO Guidelines Working Group*

[1]*Klinik und Poliklinik für Onkologie, Universitätsspital Zürich, Zürich, Switzerland;* [2]*Bern, Switzerland*

epidemiology

The crude incidence of breast cancer in the European Union is 109.9/100 000 females per year, the mortality 38.4/100 000 females per year; however, with marked geographical variation. Incidence is increasing with age and mortality is determined by initial stage and possibly treatment.

diagnosis

The diagnosis is based on clinical examination, radiological investigations (bilateral mammography and ultrasound; in particular cases MRI or other imaging techniques may be of value) and pathomorphological assessment. Pathologic diagnosis with fine needle aspiration (limited to cases with small nodules or suspicious areas) or core needle biopsy should be obtained before any surgical procedure. Final pathological diagnosis should be made according to the World Health Organization classification and the tumor–node–metastasis (TNM) (International Union Against Cancer and American Joint Comittee Cancer, sixth edition 2002) staging system analyzing all tissue removed.

staging and risk assessment

In case of preoperative systemic treatment a full clinical staging should be carried out at the outset. In case of primary surgery pathologic TNM staging based on hematoxylin and esoin staining, description of histologic type, standardized grading and evaluation of resection margins should be reported. Determination of estrogen receptor (ER) and progesterone receptor (PgR) status is mandatory, preferably by immunohistochemistry [III, B]. Reports of immunohistochemical results for ER and PgR should include the percentage of ER- and PgR-positive cells.According to the St Gallen Consensus hormone receptors are no longer included among the prognostic factors, but are the most relevant predictive factor for the choice of treatment.

**Correspondence to*: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland

Approved by the ESMO Guidelines Working Group: August 2003, last update December 2006.

Conflict of interest: Dr Pestalozzi has reported no conflicts of interest.

Immunohistochemical determination of HER2 receptor expression should be performed at the same time for treatment planning. When semi-quantitative results of immunohistochemistry are ambiguous (++), *in situ* hybridization (FISH or CISH) to determine HER2 gene amplification should be performed. It is possible to directly perform a gene amplification study (FISH or CISH) and not perform the HER2 immunohistochemistry at all.

Routine staging examinations include physical examination, full blood counts, routine chemistry including liver enzymes, alkaline phosphatase, calcium and assessment of menopausal status. This staging is needed for all patients and it can be acceptable for patients with small clinical tumors (T1) and without palpable nodes. For all other cases and in particular for candidates for pre-operative treatment the conduct of additional investigations should be considered before rather that after surgery.

In patients with higher risk (pathological N2 with four or more positive axillary nodes, or T4 tumors, or with laboratory signs or clinical signs or symptoms suspicious for the presence of metastases), chest X-ray, abdominal ultrasound and isotopic bone scan are appropriate [III, B].

Treatment decisions are based primarily on endocrine responsiveness of the tumor and secondarily on risk of recurrence. Risk stratification has been revised and currently includes three risk groups: low, intermediate and high risk (Table 1).Vascular invasion has been described as an important prognostic factor, particularly in node-negative disease.

treatment plan

The multidisciplinary discussion (possibly involving also a pathologist) leading to treatment planning should be used to integrate local and systemic therapies as well as their sequence [III, B].

The possibility of hereditary cancer should be explored and adequate counseling of relatives evaluated [IV, D].

local therapy

invasive carcinoma

Generally, operable breast cancer is treated initially by surgery, using breast-conserving surgery or mastectomy, both in

combination with axillary dissection or a sentinel node biopsy. Contraindications to breast-conserving surgery include multicentric tumors, large tumors (>3–4 cm) in small breasts, possibly retro-areolar localization and tumor-involved margins after resection. Sentinel node biopsy should only be performed in centers with documented experience and accuracy. Sentinel node biopsy should not be performed in case of palpable axillary node(s), T3 or T4 tumors, multicentric tumors, prior axillary surgery or large biopsies, after breast reconstruction or implantation of a prosthesis, during pregnancy or lactation, and after neoadjuvant systemic treatment outside of clinical trials. Breast radiotherapy is strongly recommended after breast-conserving surgery [I, A]. Post-mastectomy radiotherapy has been recommended for patients with four or more positive axillary nodes [II, B] and is suggested for T3 tumors independent of the nodal status [III, B].

ductal carcinoma *in situ* and lobular carcinoma *in situ*

When ductal carcinoma *in situ* (DCIS) is treated by breast-conserving surgery, all subgroups of patients benefit from adjuvant radiation [I, A], while tamoxifen is indicated in women with ER-positive DCIS [*II*, B] and its use in patients with ER-negative disease may be detrimental. Lobular carcinoma *in situ* (LCIS) is a risk factor for future development of invasive cancer. It should be completely resected.

primary systemic therapy

Before primary systemic therapy a biopsy for histology and analysis of predictive factors should be performed. In addition, for these higher risk patients full clinical staging to rule out metastatic disease is necessary. Primary systemic therapy is indicated for locally advanced breast cancer (stage IIIA, IIIB, IIIC) [III, B]. It can employ chemotherapy or endocrine therapy based on predictive factors similar to adjuvant treatment. If possible it should be followed by both surgery and radiotherapy and postoperative systemic treatment. Primary systemic therapy is an alternative for large operable breast cancer, to allow breast-conserving surgery [I, A].

Table 1. Definition of risk categories for patients with operated breast cancer

Low risk	Node-negative and all of the following features
	• pT ≤ 2 cm • Grade 1 • Absence of peritumoral vascular invasion • HER2 gene neither overexpressed nor amplified • Age ≥ 35 years
Intermediate risk	Node-negative and at least one of the following features: • pT > 2 cm • Grade 2 bis 3 • Presence of peritumoral vascular invasion • HER2 gene overexpressed or amplified, • Age < 35 years • Node-positive (1–3 involved nodes) • HER2 gene neither overexpressed nor amplified
High risk	Node-positive (1–3 involved nodes) • HER2 gene overexpressed or amplified • Node-positive (4 or more involved nodes)

adjuvant systemic therapy

Treatment decisions are based on two main factors: (i) estimated endocrine responsiveness of tumor tissue and (ii) risk of relapse (Table 1). Tumors with a clear or high degree of expression of ER and/or PgR are considered endocrine responsive. Patients with a total lack of ER and PgR expression in their tumors are considered endocrine non-responsive. Features indicative of uncertainty of endocrine reponsiveness include low levels of steroid hormone receptor immunoreactivity (<10% cells positive), lack of PgR, HER2 overexpression and possibly uPA and PAI-1.

Patients with tumors considered endocrine responsive may receive endocrine treatment alone (Table 2), or a combination of endocrine and chemotherapy. Patients with tumors of uncertain endocrine responsiveness are usually treated with a combination of endocrine and chemotherapy. Patients with endocrine non-responsive tumors derive greater benefit from chemotherapy and should not receive endocrine therapy. In addition to endocrine and chemotherapy, patients with HER2 overexpression or amplification should be considered for adjuvant treatment with trastuzumab (see below).

For each individual, the choice of adjuvant therapy must take into account the potential benefits, possible side-effects, and patient preference. Several decision making tools have been developed to help doctor–patient communication for adjuvant treatment decisions. Two popular tools are 'Adjuvant! Online' and the National Comprehensive Cancer Network guidelines.

endocrine therapy

Patients with tumors of likely or uncertain endocrine responsiveness should be treated with endocrine therapy (Tables 2 and 3).

Table 2. Choice of treatment modalities

Risk category	Endocrine responsiveness		
	Responsive	Uncertain	Non-responsive
Low risk	ET or nil	ET or nil	–
Intermediate risk	ET alone or CT → ET[a]	CT → ET[a]	CT
High risk	CT → ET[a]	CT → ET[a]	CT

[a]When combining chemotherapy with tamoxifen, the latter should be started after the end of chemotherapy (CT → ET) [II, A]. It is unclear whether aromatase inhibitors should be started concurrently with chemotherapy (CT + ET) or sequentially after chemotherapy (CT → ET). In premenopausal patients GnRH analogs can be started concurrently with chemotherapy, leading to rapid amenorrhea.
ET, endocrine therapy; Nil, no adjuvant systemic therapy; CT, chemotherapy.

Table 3. Treatment recommendations for 'hormone-responsive' tumors

Risk group	Premenopausal	Postmenopausal
Low	Tam, or nil, or GnRHA	Tam → AI, or AI, or Tam, or nil
Intermediate	Tam (±OS) (±CT), or CT → Tam (±OS), or Tam alone, or OS	Tam → AI, or AI, or CT → Tam → AI, o CT → AI r
High	CT → Tam, or CT → Tam + OS, or CT → (AI + OS)	CT → Tam → AI, or CT → AI

Parentheses () indicate open questions currently investigated in clinical studies.

AI, aromatase inhibitor (anastrozole, letrozole, exemestane); CT, chemotherapy; GnRHA, gonadotropin-releasing hormone analogon (goserelin); OS, ovarielle suppression; Tam, tamoxifen.

In premenopausal patients the combination of ovarian function ablation with tamoxifen, or tamoxifen alone (20 mg/day for 5 years) is indicated. Bilateral ovarectomy or irradiation of the ovaries leads to irreversible ablation of ovarian function. Gonadotropin-releasing hormone analogs (GnRHAs) (e.g. goserelin 3.6 mg s.c. monthly) generally lead to reversible ovarian suppression. They should be given for at least 2 years, but optimal duration for this treatment has not yet been established [III, D]. The adjuvant use of the combination of GnRHA and aromatase inhibitors in premenopausal patients is not currently indicated. The use of aromatase inhibitors alone must be avoided, as no evidence of efficacy is available.

In postmenopausal patients adjuvant endocrine therapy should include an aromatase inhibitor at some point in time. It is as yet undetermined whether aromatase inhibitors should be used upfront, and for which exact time period. Alternatively, tamoxifen is still an option, with a planned switch to an aromatase inhibitor after 2–3 or after 5 years. Adjuvant aromatase inhibitors increase disease-free survival when compared with tamoxifen. This has been shown for anastrozole (1 mg daily for 5 years) and for letrozole (2.5 mg daily for 5 years) given upfront [I, A], for exemestane (25 mg daily) and for anastrozole (1 mg daily) given after 2–3 years of tamoxifen [I, A] and for letrozole (2.5 mg daily) and anastrozole compared with placebo given after 5 years of tamoxifen [I, A]. The long-term cardiovascular and skeletal adverse effects associated with aromatase inhibitors are an issue of concern. Women treated with aromatase inhibitors should receive vitamin D and calcium supplements, while there is no clear evidence for the use of bisphosphonates in the adjuvant setting comcomitantly with aromatase inhibitor.

chemotherapy

Adjuvant chemotherapy for intermediate- or high-risk patients (Tables 1–3) should use a combination regimen (Table 4). In early 2006 the consensus is that such a combination should include an anthracycline, and should involve a duration of at least four cycles of treatment. The use of taxanes may be limited to high-risk patients, especially if ER-negative where data show a substantial benefit. Controversial is the use of dose-dense schedules with prophylactic G-CSF.

Table 4. Adjuvant chemotherapy

Regime	No. of cycles	Duration of cycle (weeks)
A → CMF	4 → 4 (–8)	3 → 4
CEF	6	4
AC → T	4 → 4	3 → 3
AC → T (G-CSF)	4 → 4	2 → 2
DAC	6	3
FEC → D	3 → 3	3 → 3
FEC100	6	3
A → D → CMF	3 → 3 → 3	3 → 3 → 4

A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; G-CSF, filgrastim; M, methotrexate; T, paclitaxel.

trastuzumab

Patients with HER2 overexpression (3+) or HER2 amplification can benefit from adjuvant treatment with trastuzumab. There is no evidence for the use of trastuzumab in patients with node-negative, HER2/neu-positive small (<1 cm) tumors, as in this group of patients side-effects may override possible benefits. Based on pharmacokinetic analyses a 3-weekly schedule (6 mg/kg) is considered equivalent to a weekly schedule (2 mg/kg). The standard duration of adjuvant trastuzumab has not yet been established, For the time being 1 year is recommended. Trastuzumab may be started in parallel with a taxane, but it should not be given concurrently with an anthracycline. Even when given *after* an anthracycline-containing regimen trastuzumab has cardiotoxic effects and heart function should be routinely monitored.

follow-up

History taking, eliciting of symptoms and physical examination every 3–6 months for 3 years, every 6–12 months for 3 years, then annually [A], with attention being paid to long-term side-effects, e.g. osteoporosis.

Ipsilateral (after breast-conserving surgery) and contralateral mammography every 1–2 years [D].

Not routinely recommended for asymptomatic patients: blood counts, chemistry, chest X-ray, bone scan, liver ultrasound, CT scans of chest and abdomen and any tumor markers such as CA 15-3 or CEA [I, A].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

literature

1. Goldhirsch A, Glick JH, Gelber RD et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005; 16: 1569–1583.

2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–1717.
3. Howell A, Cuzick J, Baum M et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005; 365: 60–62.
4. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005; 353: 2747–2757.
5. Jakesz R, Kaumann M, Gnant M et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and the ARNO 95 trial. Lancet 2005; 366: 455–462.
6. Coombes RC, Hall E, Gibson LJ et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 350: 1081–1092[erratum, N Engl J Med 2004; 351: 2641].
7. Goss PE, Ingle JN, Margino S et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG Ma.17. J Natl Cancer Inst 2005; 97: 1262–1271.
8. Winer EP, Hudis C, Burstein HJ et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005; 23: 619–629.
9. https://www.adjuvantonline.com/breast.jsp.
10. NCCN Clinical Practice Guidelines in Oncology Breast Cancer. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.
11. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659–1672.
12. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353: 1673–1684.
13. Joenssu H, Kollokumpu-Lehtinen P-L, Bono P et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006; 354: 809–820.